Journal of the American College of Cardiology Vol. 57, No. 25, 2011

Published by Elsevier Inc.
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.01.040

EDITORIAL COMMENT

Unraveling Myths of Platelet Function and Genetic Testing

The Road to Making Tailored Antiplatelet Therapy a Reality*

Dominick J. Angiolillo, MD, PHD

Jacksonville, Florida

Clopidogrel therapy is associated with a broad variability in pharmacodynamic (PD) response, and individuals with high on-treatment platelet reactivity (HPR) have an increased risk of recurrent ischemic events, including stent thrombosis (1,2). Given the pivotal role of this platelet-inhibiting strategy in patients with acute coronary syndrome and undergoing percutaneous coronary interventions (PCIs), numerous investigations have been conducted to identify determinants of HPR as well as cutoff values with the most meaningful prognostic implications (1,2). Recent studies have identified genetic determinants to significantly modulate PD response to clopidogrel and influence clinical outcomes (3). However, what is the additive value of individual's unmodifiable genetic makeup to a "moving target" such as platelet reactivity remains unknown. Indeed, a better understanding of this and other facets of platelet function and genetic testing may provide additional resources to better risk stratify acute coronary syndrome/PCI patients and potentially set the basis for tailored antiplatelet treatment strategies in high-risk settings with the goal of improving clinical outcomes (4).

See page 2474

In this issue of the *Journal*, Campo et al. (5) investigated profiles of on-treatment platelet reactivity over time and their relationships with genetic polymorphisms modulating clopidogrel response and clinical outcomes at 1-year in patients undergoing PCI. A total of 300 patients were studied, and PD testing by means of the point-of-care VerifyNow P2Y12 platelet function assay (Accumetrics Inc., San Diego, California) was conducted at 3 time points (before PCI, and 1 and 6 months after). Genetic determinants included the cytochrome P450 *(CYP) 2C19*2, *17, CYP3A5*3,* and *ABCB1* polymorphisms. On-treatment platelet reactivity varied in over one-quarter of patients (27.6%) during the first month after PCI, with most of these attributed to subjects initially coined as "poor responders" at the time of PCI, who subsequently became "responders" at 1 month. Genotypes explained to a certain extent (~18%) such variation. *CYP2C19*2* and **17* polymorphisms had consistent effects on PD measures, whereas *ABCB1* was more influential at baseline. On-treatment platelet reactivity was subject to minor variations after 1 month. Importantly, the serial PD evaluations determined that values of on-treatment platelet reactivity assessed at 1 month had the best prognostic value on ischemic and bleeding events. These assessments also enabled the definition of a "therapeutic window" of on-treatment platelet reactivity offering the best balance between safety and efficacy. Ultimately, the clustering of PD, genetic, and clinical information gathered from this analysis allowed the generation of a scoring system to predict HPR prognosis at 1 month and 1 year. Relevant information emerges from the present investigation that provides new and important insights in the field of platelet function and genetic testing among patients undergoing PCI that merit being emphasized.

The optimal timing of platelet function testing to predict outcomes has been a topic of debate. To date, studies have been focused on functional testing in the peri-PCI period (1,2). Indeed, knowing the results of platelet function testing before hospital discharge is more practical for the clinician, as this would potentially enable risk stratifying patients early on. However, an inferior prognostic value of a PD measure assessed in the peri-PCI period compared with that assessed at a different time point can translate into a limited benefit if a tailored treatment strategy were to be applied. The serial PD assessments conducted in the present investigation demonstrate that a considerable number of patients undergoing PCI treated with a commonly used clopidogrel dosing regimen (600-mg loading dose/75-mg maintenance dose) may be considered poor responders if testing is performed in the peri-PCI period, a finding that is in line with earlier investigations (6). The observation that functional assessments performed at 1-month follow-up more reliably reflect the true status of on-treatment platelet reactivity of a patient is also supported by its better prognostic value. These results are in line and may have had in part a contributing role to the neutral findings from the GRAVITAS (Gauging Responsiveness With a VerifyNow Assay–Impact on Thrombosis and Safety) trial (7), which failed to show any differences in 6-month outcomes in patients with HPR randomized to standard- or high-

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Department of Medicine/Division of Cardiology, University of Florida College of Medicine-Jacksonville, Jacksonville, Florida. Dr. Angiolillo reports receiving honoraria for lectures from and is on the advisory board of Bristol-Myers Squibb, sanofi-aventis, Eli Lilly, and Daiichi Sankyo; consulting fees from Bristol-Myers Squibb, sanofi-aventis, Eli Lilly, Daiichi Sankyo, The Medicines Company, Portola, Novartis Pharmaceuticals, Medicure, Accumetrics, Arena Pharmaceuticals, AstraZeneca, Merck, and Evolva; and research grants from Bristol-Myers Squibb, sanofi-aventis, GlaxoSmithKline, Otsuka, Eli Lilly, Daiichi Sankyo, The Medicines Company, Portola, Accumetrics, Schering-Plough, AstraZeneca, and Eisai.

maintenance dose of clopidogrel. In this trial, platelet reactivity was defined 12 to 24 h after PCI and notably, approximately 40% of poor-responder patients randomized to a standard clopidogrel regimen became responders at 1 month. Such change in response status may be attributed to confounding factors occurring in the peri-PCI period. Overall, these observations lead to concerns on the value of platelet function testing if performed in the peri-PCI period as well as the practicality of applying platelet function testing in clinical practice given that assessments conducted after hospital discharge, particularly if after 1 month, would have less likelihood of being performed on a broad scale. Indeed, future investigations are warranted to better understand if a narrower time frame following PCI can be identified to minimize false-positive connotations of poor-responder status. In addition, prompt identification of true poor responders is also important, given the higher risk of recurrent events in the earlier phases after PCI.

Cutoff values of on-treatment platelet reactivity that should be applied to define response status have also been subject to numerous controversies. This applies particularly to point-of-care testing devices, given that these represent the only hope for a broad-based application of platelet function testing in daily clinical practice as other assessments using light transmittance aggregometry or flow cytometry are not available in most cardiac catheterization laboratories (4). Using the VerifyNow point-of-care assay, many studies have identified $P2Y_{12}$ reactivity unit cutoff values of 230 to 240 to have the best prognostic values. VerifyNow was also used to define HPR in the GRAVITAS trial (1,7). However, the present analysis from Campo et al. (5) identified a slightly lower cutoff value, which was consistent with other studies (8). In line with this, a lower cutoff value for tailoring antiplatelet therapy was being used in the TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) trial assessing clinical outcomes in HPR patients undergoing elective PCI randomized to prasugrel or clopidogrel, which was recently halted due to the low rates of events. Indeed, patient selection, in addition to timing of assessment, can contribute to levels of platelet reactivity with different prognostic implications (9). These observations underscore that cutoff values to define patients with HPR are still not definitive and highlight the importance of pursuing further investigations to define the prognostic significance of levels of platelet reactivity according to a given clinical setting.

Furthermore, it should be kept in mind that the spectrum of response variability also denotes that certain patients may have "low" on-treatment platelet reactivity, which may increase their potential for bleeding events. Contrary to the plethora of information on the association between HPR and ischemic events, there is limited data on the prognostic implications, namely bleeding, of low platelet reactivity (10). Importantly, bleeding complications are not trivial and may carry the same weight or even more on predicting long-term mortality than a recurrent myocardial infarction, underscoring the importance of also defining levels of platelet reactivity below which this complication may occur (11). The present study was able to determine such a level and defined a "therapeutic window," using the VerifyNow assay, that delineates levels of on-treatment platelet reactivity associated with the lowest risk of ischemic and bleeding events. This had been previously determined with the Multiplate Assay (Verum Diagnostica, Munich, Germany) (12). Indeed, larger studies are needed to provide a better determination of the optimal cutoff values defining such a therapeutic window, as well as their prognostic value, which may potentially vary according to a specific clinical setting, thus enhancing the promises for tailored antiplatelet therapy.

The ever-increasing data on the impact of genetic determinants on platelet reactivity and clinical outcomes have prompted several considerations on the use of genetic testing to risk stratify patients and tailor antiplatelet therapy (13). Indeed, the unalterable status of our genetic patrimony would overcome the issues surrounding the inter- and intrapatient variability of PD measures. However, it is important to underscore that genotypes may be of limited prognostic value, as they contribute only to a small extent to the platelet phenotype and clinical outcomes (14). This leads to question if genotypes can be of adjunctive value to PD testing in risk stratifying patients. The present investigation supports that genetic and platelet function testing may represent complementary tools. Further, when results from platelet function tests and genetic tests are combined with a simple clinical parameter represented by creatinine clearance, also a marker associated with platelet reactivity (15), the investigators were able to generate a risk score algorithm to predict HPR prognosis at 1-month and 1-year follow-up. The observation that only creatinine clearance had additive value to the scoring system may be related to the fact that this overlaps with other clinical conditions. However, the small sample of the study not allowing other clinical factors to emerge as independent predictors may represent a more reliable explanation; therefore, the scoring algorithm generated from this study needs to be interpreted with caution. Indeed, larger datasets are warranted to more comprehensively generate scoring systems, as well as to validate them. Despite these limitations, this study provides important insights to help unravel some of the myths of platelet function and genetic testing and offers the premises to endure further investigations necessary to make tailoring antiplatelet therapy a reality.

Reprint requests and correspondence: Dr. Dominick J. Angiolillo, University of Florida College of Medicine-Jacksonville, 655 West 8th Street, Jacksonville, Florida 32209. E-mail: dominick.angiolillo@jax.ufl.edu.

REFERENCES

1. Bonello L, Tantry US, Marcucci R, et al., for the Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. J Am Coll Cardiol 2010;56:919–33.
2. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. J Am Coll Cardiol 2007;49:1505–16.
3. Marín F, González-Conejero R, Capranzano P, Bass TA, Roldán V, Angiolillo DJ. Pharmacogenetics in cardiovascular antithrombotic therapy. J Am Coll Cardiol 2009;54:1041–57.
4. Alfonso F, Angiolillo DJ. Platelet function assessment to predict outcomes after coronary interventions: hype or hope? J Am Coll Cardiol 2006;48:1751–4.
5. Campo G, Parrinello G, Ferraresi P, et al. Prospective evaluation of on-clopidogrel platelet reactivity over time in patients treated with percutaneous coronary intervention: relationship with gene polymorphisms and clinical outcomes. J Am Coll Cardiol 2011;57:2474–83.
6. Gurbel PA, Bliden KP, Hiatt BL, O'Connor CM. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. Circulation 2003;107:2908–13.
7. Price MJ, Berger PB, Teirstein PS, et al., for the GRAVITAS Investigators. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention: the GRAVITAS randomized trial. JAMA 2011;305:1097–105.
8. Campo G, Fileti L, de Cesare N, et al., for the 3T/2R Investigators. Long-term clinical outcome based on aspirin and clopidogrel responsiveness status after elective percutaneous coronary intervention: a 3T/2R (Tailoring Treatment With Tirofiban in Patients Showing Resistance to Aspirin and/or Resistance to Clopidogrel) trial substudy. J Am Coll Cardiol 2010;56:1447–55.
9. Angiolillo DJ, Bernardo E, Sabaté M, et al. Impact of platelet reactivity on cardiovascular outcomes in patients with type 2 diabetes mellitus and coronary artery disease. J Am Coll Cardiol 2007;50:1541–7.
10. Ferreiro JL, Sibbing D, Angiolillo DJ. Platelet function testing and risk of bleeding complications. Thromb Haemost 2010;103:1128–35.
11. Pocock SJ, Mehran R, Clayton TC, et al. Prognostic modeling of individual patient risk and mortality impact of ischemic and hemorrhagic complications: assessment from the Acute Catheterization and Urgent Intervention Triage Strategy trial. Circulation 2010;121:43–51.
12. Sibbing D, Steinhubl SR, Schulz S, Schömig A, Kastrati A. Platelet aggregation and its association with stent thrombosis and bleeding in clopidogrel-treated patients: initial evidence of a therapeutic window. J Am Coll Cardiol 2010;56:317–8.
13. Damani SB, Topol EJ. The case for routine genotyping in dual-antiplatelet therapy. J Am Coll Cardiol 2010;56:109–11.
14. Gurbel PA, Tantry US, Shuldiner AR, Kereiakes DJ. Genotyping: one piece of the puzzle to personalize antiplatelet therapy. J Am Coll Cardiol 2010;56:112–6.
15. Angiolillo DJ, Bernardo E, Capodanno D, et al. Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. J Am Coll Cardiol 2010;55:1139–46.

Key Words: clinical outcome ■ clopidogrel ■ gene polymorphism ■ P2Y12 VerifyNow ■ platelet reactivity.